



AN R&D BLUEPRINT FOR ACTION TO PREVENT EPIDEMICS

**FUNDING & COORDINATION MODELS FOR
PREPAREDNESS AND RESPONSE**
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**Being ready for the next epidemic:
How to improve R&D funding for preparedness and response
to emerging pathogens**

An exploration of different funding and coordination models in the framework of the
WHO R&D Blueprint for action to prevent epidemics

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The Blueprint consists of five different workstreams. This publication is the outcome of workstream 5 that focused on the exploration of funding models for preparedness and response. It has been developed under the oversight of the Scientific Advisory Group for the Blueprint process that provided very valuable feedback.

For further information on the R&D Blueprint, please visit:
<http://www.who.int/csr/research-and-development/en/>

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Executive summary

The 2014-15 Ebola outbreak reminded the public health community that the world is ill-prepared to avert major outbreaks of emerging pathogens. The WHO R&D Blueprint for action to prevent epidemics addresses the question of how to improve R&D preparedness and response, focusing on a list of priority diseases in line with recommendations from a number of expert Panels and Commissions. The development of vaccines, therapeutics and diagnostics is costly. Based on recent research, this report presents estimates of the funding needed to develop drug and vaccine candidates as well as diagnostics, taking into account average failure rates in the development process. These numbers allow a rough estimate of the cost of preparedness, with a sufficient number of drug and vaccine candidates developed for the different pathogens included in the Blueprint. As most of the pathogens prioritised by the Blueprint are poorly researched, it is estimated that up to \$1.17bn would have to be invested for each pathogen, although R&D could be considerably cheaper, if built on existing technologies.

An essential condition for better R&D preparedness and response is the availability of funding. However, there is currently insufficient funding to cover the required R&D to address pathogens included in the Blueprint. New and innovative funding models are needed to more sustainably fund R&D for emergency response and preparedness. In previous years, many different innovative funding models have been discussed for R&D for neglected diseases and other poverty-related illnesses.

This report presents options on how to ensure that the required research activities are financed and take place in the most efficient way, involving all necessary stakeholders. The *Consultation on Financing for R&D preparedness and response to public health emergencies due to highly infectious pathogens* in Oslo highlighted the need to start quickly, with the focused objective of defining target product profiles for medical products to address a specific set of the identified pathogens. One of the Consultation's recommendations was to seek mechanisms to ensure sustainable financing, starting by engaging those stakeholders who are ready to move. Discussions in different fora such as the G7 and the G20 and the UN General Assembly are ongoing and will hopefully result in the creation of a funding mechanism.

However, while it is important to work towards more sustainable R&D funding, there is also a need for short-term action. To that end, the Blueprint explores possible ways to make more efficient use of existing funding through better coordination, using the experience from the pilot project on Middle East respiratory syndrome coronavirus (MERS-CoV) and the experience gained with R&D coordination in the development of malaria vaccines.

Part 1: Scope of the Blueprint and objective of workstream 5 – Exploration of funding models for preparedness and response

1.1 Scope of the Blueprint

In May 2015, the Sixty-Eighth World Health Assembly

“...welcomed the development of a blueprint, in consultation with Member States and relevant stakeholders, for accelerating research and development in epidemics or health emergency situations where there are no, or insufficient, preventive, and curative solutions, taking into account other relevant work streams within WHO”¹.

The overall objective of this blueprint is as follows:

- (i) To make the case for increased investment in research and development (R&D) by the public, private and philanthropic sectors
- (ii) To make better use of existing investments by identifying priority needs for each pathogen, so that funders can focus on the most necessary and promising projects, and align their agendas to tackle these priorities.

The Blueprint currently being developed by WHO consists of five workstreams:

- Workstream 1: Prioritization of pathogens and operational plan
- Workstream 2: Identification of research priorities
- Workstream 3: Coordination of stakeholders and expansion of capacity
- Workstream 4: Assessment of preparedness and impact of intervention
- Workstream 5: Exploration of funding models for R&D preparedness and response.

This document is the outcome document for workstream 5. An earlier version served as a background paper for the *Consultation on Financing for R&D preparedness and response to public health emergencies due to highly infectious pathogens* that was organized jointly by WHO and the Norwegian Institute of Public Health in Oslo in October 2015. The feedback received during this consultation has been integrated into this outcome document.² Overall, the consultation concluded that adequate and sustainable investment and new incentives are urgently needed to ensure appropriate funding for R&D preparedness and response. This conclusion is in line with the recommendations of a number of Panel and Commission reports published in the wake of the 2014-15 Ebola outbreak, as illustrated in Box 1.

¹ Decision WHA68(10).

² Outcome document of the consultation: <http://www.who.int/medicines/ebola-treatment/Outcome.pdf?ua=1>

Box 1: Expert group demands to WHO for pandemic preparedness R&D

In the wake of the 2014-15 Ebola outbreak, various reports on how to avert similar crises in the future have been published, addressing among other things the question of how to improve R&D preparedness and response:

The **Ebola Interim Assessment Panel** recommends that “WHO should play a central convening role in research and development efforts in future emergencies, including the acceleration of the development of appropriate diagnostics, vaccines, therapeutics and medical and information technology”.³

The **High-level Panel on the Global Response to Health Crises** recommends that “...WHO oversees the establishment and management of an international fund” to support R&D efforts for prioritized pathogens⁴.

The **Commission on a Global Health Risk Framework for the Future** sees WHO in a leading role in galvanizing R&D for pandemic preparedness through the creation of a Pandemic Product Development Committee⁵.

The **Independent Panel on the Global Response to Ebola**, a group of 19 experts convened by the London School of Hygiene & Tropical Medicine (LSHTM) and the Harvard Global Health Institute, published a set of ten recommendations, calling among other things for WHO to assist in establishing “a global fund to finance, accelerate and prioritize R&D”.⁶

The Oslo Consultation highlighted the need to start quickly, with the focused objective of defining target product profiles (TPPs) for a specific set of emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist. This list of pathogens for which action is particularly urgent has been finalized by workstream 1⁷ (Box 2).

³ *Report of the Ebola Interim Assessment Panel*, July 2015, <http://www.who.int/csr/resources/publications/ebola/ebola-panel-report/en/>

⁴ *Protecting humanity from future health crises*. Report of the High-level Panel on the Global Response to Health Crises. January 2016. http://www.un.org/News/dh/infocus/HLP/2016-02-05_Final_Report_Global_Response_to_Health_Crises.pdf

⁵ *The neglected dimension of global security*. Report of the Commission on a Global Health Risk Framework for the Future, January 2016. <http://nam.edu/wp-content/uploads/2016/01/Neglected-Dimension-of-Global-Security.pdf>

⁶ Will Ebola change the game? Ten essential reforms before the next pandemic. Report of the Harvard LSHTM Independent Panel on the Global Response to Ebola. Moon et al. *The Lancet*, 386 (10009), 2204-21

⁷ <http://www.who.int/csr/research-and-development/workstream1-prioritize-pathogens/en/>

Box 2: Priority list of diseases defined by the Blueprint

- Crimean Congo hemorrhagic fever
- MERS-CoV disease
- Ebola virus disease
- Nipah virus infection
- Zika virus disease
- Severe fever with thrombocytopenia syndrome
- Lassa fever
- SARS-CoV disease
- Marburg hemorrhagic fever
- Rift Valley fever
- Chikungunya fever

The Oslo consultation also recommended a search for mechanisms to ensure sustainable financing, starting by engaging those stakeholders that are ready to move. This requires high-level political commitment to kick-start the process, the presence of which would be likely to motivate others to join. The presentation of the Blueprint at the World Health Assembly in May 2016 will provide an opportunity to act. The consultation highlighted the need to:

- (i) Increase investment in R&D for emergency preparedness, as better preparedness could significantly cut R&D and other costs during response
- (ii) Improve alignment of different R&D efforts to address identified global priorities
- (iii) Ensure more efficient use of existing funding mechanisms, by avoiding duplication of efforts.

1.2 Scope of workstream 5

Workstream 5 deals with the question of how to ensure adequate and sustainable funding for the research needs identified by workstreams 1 and 2. This includes the funding of research for preparedness as well as for response in an emergency situation. This paper explores different options on how to ensure that the required research activities are financed and are taking place in the most efficient way, involving all necessary stakeholders. This can be achieved by different means, including:

- (i) Better use of existing funding through enhanced coordination
- (ii) Reinforcement and expansion of existing mechanisms and organizations that fund related research
- (iii) The creation of new mechanisms.

In past years many different innovative funding models have been discussed for R&D for neglected diseases and other poverty-related illnesses. These have included such different forms as taxes on financial transactions and weapons sales, or an airfare levy. These and other mechanisms have also been proposed—and partly utilized—for several other development issues. This paper does not review all such possible financing mechanisms: these have already been analysed in the context of financing R&D in neglected diseases, by the WHO Expert Working Group on Research and Development Financing⁸ and the WHO Consultative Expert

⁸ See the Report of this Group: http://www.who.int/phi/documents/ewg_report/en/

Working Group on Research and Development: Financing and Coordination (CEWG)⁹. Any new funding mechanism should take into account the main principles for equitable R&D as proposed by the CEWG: open knowledge innovation and the delinkage of R&D from product costs in order to ensure affordability.

Part 2: Investment case and funding needs

2.1 Status quo: limited incentives for investing in R&D

In a situation comparable to that facing neglected tropical diseases, the market-driven innovation system does not provide sufficient incentives for the private sector to invest in R&D on highly infectious emerging pathogens. The current system provides incentives for development of new medicines and other health products only where there is a sufficient predictable market, and where inventors can expect a return on investment. With most, if not all, of the emerging pathogens covered by the Blueprint, this is not the case.

Outbreaks are not predictable; they often take place in poor countries and/or remote rural areas, and are usually contained quickly. As a consequence, market mechanisms provide too little investment in R&D for new medicines, diagnostics and vaccines for these pathogens. Even when taking publicly funded research into account, we fall short, since public investment often focuses on the health needs of developed countries and early stage discovery rather than the costly clinical development of new technologies. Overall, investment remains insufficient to ensure preparedness and implement the R&D priorities identified in workstream 2.

However: as the Oslo consultation and the Panel and Commission reports (Box 1) confirmed the need for adequate and sustainable investment into R&D, new incentives are urgently needed to ensure appropriate funding for R&D preparedness and response.

2.2 Case for investment in R&D for preparedness

Seen from the perspective of global economy and public health rather than that of a private investor, financing R&D for preparedness is clearly a sound investment. Despite the fact that development of new medical products in general requires considerable upfront investment and outcomes are uncertain, costs are much lower than those associated with a large-scale outbreak of any of the diseases covered by the Blueprint. This was demonstrated by the recent outbreak of Ebola Virus Disease in West Africa, during which—as of march 2016—there have been over 28,000 reported cases of Ebola Virus Disease, mostly in Guinea, Liberia, and Sierra Leone, with over 11,000 reported deaths. The epidemic crippled the economies of all three countries, with a projected total GDP loss for 2015 of US\$2.2bn.¹⁰

⁹ See the Report of this Group: http://www.who.int/phi/cewg_report/en/

¹⁰ World Bank Group: *Update on the economic impact on the 2014-2015 Ebola epidemic on Liberia, Sierra Leone and Guinea*, Report #95804, April 2015.

Ebola was not the first reminder that pandemics are costly. Between 1997 and 2009, six major outbreaks of highly fatal zoonoses led to estimated economic losses of US\$80bn. For example, between November 2002 and July 2003, 8096 people worldwide became sick with severe acute respiratory syndrome coronavirus (SARS-CoV) disease of whom 774 died¹¹. The most significant economic impact of this outbreak was felt in four East Asian economies: the Republic of Singapore; the People's Republic of China; China Hong Kong SAR; and Taiwan, China. Estimated total GDP loss in 2003 for the four economies amounted to about US\$13bn¹².

In light of these economic losses, it is clear that increased investment in preparedness pays off if it mitigates the risk of future outbreaks. For example, the immediate availability of an easy-to-use point-of-care diagnostic tool for Ebola Virus Disease would have helped enormously to control infection by identifying those infected and enabling them to be safely isolated.

2.3 Funding needs for the implementation of the Blueprint

Funding needs for the implementation of the Blueprint can be separated into funding R&D to ensure preparedness ahead of an outbreak, and funding R&D during emergency situations.

a) Funding research to ensure preparedness ahead of an outbreak

The individual assessments of product pipelines that will be done under workstream 2 will allow the evaluation of the financial needs for each pathogen. This assessment will include the development of medicines, vaccines, and diagnostics as well as protective gear and/or other necessary medical equipment. Some of these products will be specific to a certain pathogen; others will be cross cutting, such as platform technologies, for example for vaccine development. Depending on the needs identified, this can also include development of technological support tools—for example, mobile applications to exchange information, or software to facilitate contact tracing. Cross-cutting research is another area where more work is needed. Examples include veterinary research of related zoonoses, research into health systems, and anthropological and social science studies to prepare for the socio-cultural and political dimensions of any outbreak, allowing for the design of interventions adapted to local customs and cultures.

b) Funding for R&D as part of the response in an emergency situation

This section includes funding of Phase II and III clinical trials of candidate vaccines or medicines, as well as operational research regarding transmission, identification of sources and appropriate treatment in general. For example, in the case of airborne diseases, this could include trials on the effectiveness of masks and respirators for infection control. Emergency response R&D requires the rapid availability of funds because clinical trials and other research should start as early as possible. One objective of the Blueprint is to reduce the time span between the start of an outbreak and start of trials to four months. If this had been achieved in the Ebola outbreak in West Africa, it is likely that Phase III vaccine trials could have been finalized before the containment of the outbreak.

¹¹ WHO: *Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003* (based on data as of the 31 December 2003).

¹² World Bank: *On SARS type economic effects during infectious disease outbreaks*. Policy Research Working Paper 4466, January 2008.

Funding for R&D preparedness and funding as part of outbreak response are different in nature. While preparedness allows for long term planning, response requires immediate availability of funds and fast decision-making. As we have learned from previous outbreaks, financial means do become available in health emergencies, allowing for R&D measures to be financed at least to a certain extent. However, there is need for a bridging mechanism that would cover the first few months during an outbreak, to make funds immediately available and to ensure that the time span between the outbreak and the start of clinical trials could be reduced as much as possible. This must go hand in hand with a decision-making process that allows for a fast response. Workstream 3 will develop the necessary tools with which to achieve this, such as draft clinical trial protocols and agreements, and agreed data collection protocols adapted for emergency situations.

c) How much funding is needed?

One outcome following the publication of the CEWG¹³ report was a request from the World Health Assembly¹⁴ to the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) to investigate how a financial mechanism to support health product R&D under WHO could be developed. In response, TDR published a report that provides estimates for the minimum funding required to develop different interventions including vaccines, drugs and diagnostics (see Box 3 for methodological details)¹⁵.

Box 3: Development costs in the TDR Portfolio-to-Impact model (P2I)

TDR used a novel method to estimate the average development costs of health interventions for neglected diseases¹⁵. Specific assumptions were developed for each product archetype, from diagnostics, through vaccines to drugs (see table below¹⁵). Assumptions were based on a bottom-up analysis of clinical trial costs and a review of attrition rates and cycle times for over 25,000 development candidates in neglected diseases R&D between 2007 and 2014¹⁶. These assumptions were further refined and validated based on academic literature^{17,18}, industry publications¹⁹, and consultations with several Product Development Partnerships (PDPs), biopharmaceutical and diagnostic industry players and major donor organizations. The numbers take into account direct expenses, clinical supplies, internal headcount costs and non-monetary in-kind contributions. They do not include costs from basic research to lead optimization; GMP manufacturing infrastructure- and scale-up costs; manufacturing; regulatory or registration fees; all post-market commitments; or capacity building. The model

¹³ See the Report of this Group: http://www.who.int/phi/cewg_report/en/

¹⁴ WHA67(15) page 8, http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_DIV3-en.pdf

¹⁵ *Health product research & development fund: a proposal for financing and operation*. UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (Geneva, 2016). http://apps.who.int/iris/bitstream/10665/204522/1/9789241510295_eng.pdf?ua=1

¹⁶ Citeline. Pharmaprojects database 2015: <https://citeline.com/products/pharmaprojects/> (2016/02/11)

¹⁷ Liao XC. Early development of antibody therapeutics: key aspects of advancing an antibody drug from research to clinic. *Trends in Bio/Pharm. Ind.* 2009;18–23 (http://www.tbiweb.org/tbi/file_dir/TBI2009/Early%20development.pdf, accessed 28 January 2016).

¹⁸ Horvath C. *Comparison of preclinical development programs for small molecules and large molecules studies, timing, materials, and costs*. Ed: Cavagnaro JA. Hoboken, NJ: John Wiley & Sons, Inc.; 2010.

¹⁹ PAREXEL Biopharmaceutical R&D Statistical Sourcebook: Parexel; 2014.

was developed for neglected diseases. Some factors—such as the need for high-security research facilities for certain highly infectious diseases— might significantly increase costs for R&D on blueprint pathogens. All numbers are average estimates, and the costs for individual cases can vary substantially.

Archetypes		Description	Examples
New Vaccine	Simple	Platform has been used to develop other vaccines	Hepatitis A/B, Polio
	Complex	Requires completely novel approach/no platform, no existing research	Pneumococcal conjugate vaccines (PCV), Meningitis B
Drug repurposing	Simple	Drug has sufficient safety data to start development in phase II	Azithromycin (trachoma), doxycycline
	Complex	Drug requires some phase I clinical trials to verify safety in humans	Moxidectin
New chemical entity (NCE)	Simple	Validated target/mechanism of action	Primaquine
	Complex	Novel target/mechanism of action without understanding of disease pathogenesis	Imatinib
Diagnostic	Assay development	Development of a diagnostic assay	Lateral flow tests, qualitative/quantitative molecular tests
	Simple platform development	Development of platform that enhances current technology	Hypersensitive malaria RDT

Table 1 summarises the minimum funds needed for each phase of development. The amount of funding needed for each pathogen largely depends on how much is already known about that pathogen, and whether there are already technologies against related pathogens that can be built upon (e.g. dengue vaccines for Zika, or R&D on Ebola for Marburg). This is reflected in the archetypes for each product: simple forms of an intervention can build on previous technologies and mechanisms of action, whereas complex new vaccines or drugs require more early stage research and involve higher risks of failure.

The development costs up to the end of clinical phase I are essential for R&D preparedness for emerging pathogens: as phase II+III studies can only be carried out during an outbreak, preparedness aims to have a sufficiently high number of candidates in the pipeline that can be evaluated rapidly in an emergency. The size of this portfolio depends on the attrition rates specific to each product archetype and can be obtained from table 1 by looking at the candidates needed to start phase II clinical trials. For example, if phase II trials are started with 4 simple vaccines, 2 of them will statistically make it to phase III and one registered product would be obtained in the end – on average. Developing a portfolio of interventions that successfully completed phase I would thus cost between \$53m (4 repurposed drugs), \$65m (4 simple NCEs) and \$553m (13 complex NCEs) for drugs; and roughly between \$85m (4 simple candidates) and \$619m (8 complex candidates) for vaccines. Thus, estimates for total preparedness costs (drugs and vaccines) per pathogen start at \$133m – if a disease is well understood and technologies exist to build upon. As this is not the case for most pathogens included in the Blueprint, the

necessary funds are likely towards those needed to develop complex archetypes, amounting to up to \$1.17bn. This estimate does not include a number of expenses (see Box 3) such as the build-up and maintenance of the necessary R&D infrastructure.

Table 1: Estimated costs of development for different interventions, disaggregated by stage of development. All cost values in million US\$. In general, these numbers confirm that failing early means failing cheap. Thus, the more successfully the pipeline is narrowed down to the most promising candidates, the more costs can be reduced. The number of candidates needed per phase was calculated using the success rate for each phase and rounding up, with the aim of obtaining one registered product at the end of the process (example: to get one registered complex vaccine: $1/0.64$ (success rate for phase III) = 1.56. Rounded up: 2 candidates needed for phase III. The calculation for the preceding phase is done with the unrounded number). Risk-adjusted costs were calculated by multiplying the number of candidates needed per phase with the cost per candidate²⁰. Data on costs per phase and attrition rates were provided by TDR (publication in preparation). TDR's P2I model (see Box 3 for methodological details) does not provide risk-adjusted product development costs for each product archetype.

		Preclinical				Phase I				Risk-adjusted until phase I	Phase II				Phase III				Total Risk-adjusted
		per candidate	success rate	# of candidates	risk-adjusted	per candidate	success rate	# of candidates	risk-adjusted		per candidate	success rate	# of candidates	risk-adjusted	per candidate	success rate	# of candidates	risk-adjusted	
Vaccines	simple	\$ 6.7	41%	11	\$ 73.7	\$ 2.2	68%	5	\$ 11.0	\$ 84.7	\$13.2	46%	4	\$ 52.8	\$111.1	71%	2	\$ 222.2	\$ 359.7
	complex	\$16.6	41%	35	\$581.0	\$ 2.5	50%	15	\$ 37.5	\$ 618.5	\$13.9	22%	8	\$111.2	\$133.3	64%	2	\$ 266.6	\$ 996.3
Drug repurposing	simple	N/A				N/A					\$ 5.8	46%	4	\$ 23.2	\$ 17.6	68%	2	\$ 35.2	\$ 58.4
	complex	\$ 5.0	75%	8	\$ 40.0	\$ 2.2	59%	6	\$ 13.2	\$ 53.2	\$ 5.8	46%	4	\$ 23.2	\$ 17.6	68%	2	\$ 35.2	\$ 111.6
NCEs	simple	\$ 5.0	65%	10	\$ 50.0	\$ 2.2	60%	7	\$ 15.4	\$ 65.4	\$ 5.8	39%	4	\$ 23.2	\$ 32.8	70%	2	\$ 65.6	\$ 154.2
	complex	\$10.0	55%	39	\$390.0	\$ 7.4	58%	22	\$162.8	\$ 552.8	\$ 6.3	20%	13	\$ 81.9	\$ 36.1	40%	3	\$ 108.3	\$ 743.0
		Selection & validation of markers				Development					Regulatory trials								
Diagnostics	Assay development	\$ 3.0	50%	2	\$ 6.0	\$ 2.0	100%	1	\$ 2.0		\$ 3.5	100%	1	\$ 3.5					\$ 11.5
	Simple platform development	N/A				\$ 100	75%	2	\$200.0		\$ 3.5	100%	1	\$ 3.5					\$ 203.5

²⁰ This method has been used previously, e.g. by Czaplewski, L. et al. (2016). Alternatives to antibiotics — a pipeline portfolio review. *Lancet Infectious Diseases* 3099:1–13.

The development of diagnostics is also crucial for an effective emergency response. According to the TDR model, simple, rapid diagnostic tests are estimated to cost around \$11.5m to develop, while hospital-based platform diagnostics are more expensive, with estimated development costs of around \$200m. However, these platforms, once developed, would then be adaptable for diagnosis of other pathogens. Depending on the individual pathogen and the various possibilities for use of existing platforms, these costs may be lower for specific cases. Whether it is feasible to develop disease-specific tests ahead of a major outbreak depends on the variability of each pathogen – if a diagnostic can only detect certain strains of a pathogen, it might be useless when a pandemic is caused by another strain.

In addition, further resources are needed for setting up production and distribution, and are not included in these assumptions. These costs include the development of a GMP production line, the building of human capacity, and the eventual deployment of the product (Box 4). It is estimated that setting up a public multi-product manufacturing facility for a portfolio of vaccines and biologicals in the US would cost around \$750m, with maintaining costs of around \$250m annually²¹. However, a facility solely dedicated to vaccines would require a more modest investment. The study focuses on costs if such a facility would be built in the US. Setting it up in a low- or middle income country with the appropriate GMP infrastructure would likely be considerably cheaper.

Box 4: Costs for deploying vaccines

During the 2014/15 Ebola outbreak, WHO started clinical trials of an experimental Ebola vaccine. Based on this experience, deployment costs for vaccines are estimated as follows (based on a cost of US\$50 per vaccine, and US\$100 for the numbers in brackets, respectively):

1,000 persons:	US\$0.9m (1.0m)
10,000 persons:	US\$1.7m (2.3m)
100,000 persons:	US\$11.1m (17.3m)

These numbers are based on the following set of assumptions: person-to person transmission of the pathogen; implementation of a risk-based vaccination strategy (e.g. the ring vaccination strategy); the requirement to keep vaccines at -80°C; and a 20% wastage rate. The cost is all-inclusive for vaccination activities and comprises bundled vaccine costs, operations and infrastructure, training, and technical assistance. Surveillance and other response costs are not included.

²¹ *Ensuring Biologics Advanced Development and Manufacturing Capability for the United States Government: A Summary of Key Findings and Conclusions*. Cooperative Agreement Research Study between Defense Advanced Research Projects Agency (DARPA) and University of Pittsburgh Medical Center (UPMC). (2009)

Part 3: Options to increase levels and coordination of funding

In general, measures to create financial resources for R&D can be divided into mechanisms relying completely on public funding and mechanisms that also leverage private contributions. The latter include instruments such as prize funds, milestone prizes and purchase commitments, and will be discussed in part 4. In this section, possibilities for securing sustainable public funding are explored separately for R&D to ensure preparedness (3.1) and R&D in emergency situations (3.2). How to best allocate and distribute funds to maximize return on investment must also be explored, and depends on the disease as well as how research is being carried out, and by whom²².

3.1 Funding of R&D to ensure preparedness

Ensuring adequate investment in R&D is not only a question of increasing funding. Equally important is ensuring that any existing and additional funding is spent efficiently to address the global public health R&D needs identified by the Blueprint. Thus, the overall objectives are:

- Increase overall investment into R&D for emergency preparedness
- Align different R&D efforts to address the global priorities as identified by the Blueprint
- Ensure efficient use of existing funding.

While the first point addresses funding directly, the other two focus on coordination of effort. The fragmented research landscape includes academia, industry and public research institutes; the similarly fragmented landscape of possible funding sources—and the absence of coordination of who is doing what and what gets funded—leads to inefficiencies. Increased coordination and alignment against identified R&D priorities would contribute to a more efficient use of scarce resources. This is not unique to R&D on highly infectious emerging pathogens, and efforts have been made in past years to improve coordination of research funding in other areas, notably neglected diseases²³. There are different models that could be used to achieve these goals. These are addressed in the following paragraphs.

a) Coordination of individual funders on product and/or pathogen level

One possibility for coordination of R&D is the alignment of different funders' research priorities in certain research areas, with distinct funding entities for specific pathogens, groups of pathogens, or products. This could be done through a series of matching events assembling relevant funders and researchers, organized by a trusted convener, for each of the pathogens or groups of pathogens. Based on the research priorities identified by the Blueprint, the objective would be to convince funders to “divide” different tasks among themselves in a coordinated fashion, resulting in specific work-sharing agreements organized according to different pathogens or products. This could be done on a small scale level—for example by product for a specific disease—or at a higher level, for example with one country committing to ensure the

²² Renwick, M.J., Brogan, D.M. & Mossialos, E. (2016). A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. *The Journal of antibiotics* **69**:73–88.

²³ CEWG report: http://www.who.int/phi/cewg_report/en/

implementation of all identified research priorities for one pathogen or group of pathogens. The convener of these meetings would also be responsible for monitoring progress and regular reporting of results.

Funders engage with researching entities following their own rules. This allows engagement of funders who cannot—due to formal or other constraints—engage in pooled funding. There are also examples for such coordination in biomedical R&D: for example, the Malaria Vaccine Funders Group has been guiding R&D at product level and first published a continuously updated roadmap in 2006 (Annex 1, Box 8). In the context of this Blueprint, a group of key funders drafted a similar roadmap for R&D on diagnostics, vaccines and treatments for MERS-CoV, at a gathering facilitated by WHO (see part 5). Currently, there are also efforts to coordinate research on Zika virus disease: Experts from different fields and funders are consulting intensively—again convened by WHO—to identify the most urgent research needs and discuss priorities for product development²⁴. The Global Research Collaboration for Infectious Disease Preparedness network (GloPID-R; Annex 1, Box 7) is another good example of this approach: GloPID-R members map research and identify gaps in four crucial research areas: aetiology, diagnostics, vaccines, and vector control. This enables them to target funding in a coordinated manner, and to link new and existing research projects where synergies exist.

Whether such active coordination should be organized around a pathogen, a group of pathogens, a platform technology or a single product depends on the complexity of the R&D challenge and the number of entities involved. Once workstream 2 has identified the respective priorities for each pathogen, starting with MERS-CoV, this should be discussed through an overarching coordination mechanism—possibly in the form of a scientific advisory committee or a board—required for the implementation of the Blueprint.

b) Coordination through joint programming

Another approach to research coordination is joint programming; a mechanism where research funders agree on certain priorities, and allocate funding based on a common strategy and joint or separate calls for proposals, without pooling financial resources. The oversight of individual research programs and projects remains in the responsibility of the individual agencies, but all are aligned according to the joint research strategy. One example is the European Union's Joint Programming Initiative on Antimicrobial Resistance (Annex 1, Box 6).

Joint programming allows for priority-setting across different diseases as research funders commit to allocate money to agreed fields of R&D. For the Blueprint, this would require the formation of a group in which all relevant research funding agencies are represented. This group, assisted by a small secretariat, would agree on its members' research agendas in line with priorities identified by the Blueprint, and implement them through joint calls for proposals.

²⁴ WHO global consultation on research related to Zika virus infection:
<http://www.who.int/csr/research-and-development/consultations/zika-research/en/>

c) Pooled financing on global level

Another potential mechanism to increase funding and improve coordination is the establishment of a pooled fund. Funders pool their contributions on a voluntary or mandatory basis in a centrally managed entity that disburses funds according to identified research priorities. Pooled funding is recommended by the High-level Panel on the Global Response to Health Crises; the LSHTM/Harvard Independent Panel; and the Commission on a Global Health Risk Framework for the Future. The High-Level Panel also advises that:

“...the WHO oversees the establishment and management of an international fund of at least \$1 billion per annum to support R&D of vaccines, therapeutics and rapid diagnostics for neglected communicable diseases”²⁵.

However, the report leaves open the question of who should contribute to this fund and whether payments should be mandatory. Similarly, the LSHTM/Harvard Global Health Institute Independent Panel on the Global Response to Ebola recommends financing and prioritization by a pooled global fund to accelerate R&D on emerging pathogens²⁶. Thirdly, the Commission on a Global Health Risk Framework for the Future suggests the creation of a Pandemic Product Development Committee (PPDC)²⁷, a proposed mixture of a joint programming initiative and a pooled fund. The PPDC should identify R&D gaps, help mobilize funds, and prioritize across different diseases; but is also partly responsible for the deployment of contributions. The commission suggests that the PPDC be managed by a technical governing board of experts and supported by WHO.

The benefit of a pooled fund is that it provides a single mechanism through which to share the risks and cost of funding R&D in priority health areas. Pooled arrangements can also be more efficient than large uncoordinated groups of small independent funders. A pooled funding mechanism is also useful for smaller funders/countries that lack the capacity to set up independent programmes, but which also want to contribute to investments in this area given the global nature of the challenge. A pooled arrangement can also lower researchers' opportunity costs with respect to administration, as they deal with only one funder, and can allow more systematic introduction of new, innovative financing models. The High-level Panel on the Global Response to Health Crises and the Oslo Consultation both suggest that, if well financed, a pooled fund could cover R&D for preparedness and response.

On the other hand, a pooled funding mechanism requires the readiness of funders and countries to entrust financial resources to an entity over which they have limited or no control. Typically, not all potential funders are able or willing to submit to such an arrangement.

²⁵ *Protecting Humanity from Future Health Crises*. Report of the High-level Panel on the Global Response to Health Crises. January 2016. http://www.un.org/News/dh/infocus/HLP/2016-02-05_Final_Report_Global_Response_to_Health_Crises.pdf

²⁶ Will Ebola change the game? Ten essential reforms before the next pandemic. Report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola. Moon et al. *The Lancet*, 386(10009), 2204-21

²⁷ *The neglected dimension of global security*. Report of the Commission on a Global Health Risk Framework for the Future, January 2016. <http://nam.edu/wp-content/uploads/2016/01/Neglected-Dimension-of-Global-Security.pdf>

For voluntary funds, financial sustainability is a challenge, but entities such as the Global Fund and Gavi, the Vaccines Alliance have shown that it is possible using—among other things—a replenishment mechanism. This approach is, however, likely to be more challenging for financing R&D, as it offers no short-term success and return on investment and requires considerable financial input. Finally, while overall administrative costs may be lower than those for running many small national research programmes, the central administration of any pooled funding mechanism also requires financial resources. Thus, there is a minimal size for a fund if it is to be cost-efficient (Figure 1). The Commission on a Global Health Risk Framework for the Future estimates that an additional US\$1bn from different sources (see Box 5) would be needed to provide effective support for R&D for pandemic preparedness.

Several options for pooled funds have been proposed recently, including the establishment of a global R&D fund and a Global Vaccine Development Fund (Annex 1, Box 9).

The CEWG had suggested a mandatory funding mechanism for R&D into neglected diseases. WHO member states agreed to explore the possibility of setting up a voluntary pooled fund hosted at TDR (Annex 1,

Box 10). Options for this fund will be debated at an open-ended Member States meeting in May 2016. To inform this meeting, TDR recently published a report presenting options for operation and financing of a sustained health product R&D fund²⁸; the mechanism is not disease-specific and the envisaged scope of diseases (Type II and Type III diseases and the specific R&D needs of developing countries in relation to Type I diseases) includes the pathogens covered by the Blueprint²⁹.

All Blueprint pathogens are Type II (diseases present in both rich and poor countries, but with a substantial proportion of the cases in poor countries) or Type III (diseases overwhelmingly or exclusively present in poor countries). Sustainable financing of the fund is a critical point and a mechanism would be required that ensures regular replenishment at a level allowing financing of research activities for both neglected diseases and the priorities identified by the Blueprint. The TDR report presents how many new products can be expected for different fund sizes (Figure 1), elaborates on operational considerations, and provides a toolkit for portfolio management.

²⁸ "Health Product Research & Development Fund: A Proposal for Financing and Operation" UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (Geneva, 2016).

²⁹ WHO background document on disease types: http://www.who.int/phi/3-background_cewg_agenda_item5_disease_types_final.pdf



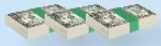

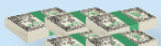

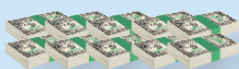



ANNUAL FUND SIZE US\$ millions (m) ^a		STEADY STATE PROJECTS/YEAR	ESTIMATED STAFFING NEEDS (FULL-TIME EQUIVALENT)	IF DEVELOPMENT STARTS IN 2017, WHAT IS EXPECTED BY 2030?
1	Passive coordination Up to US\$ 1 m	Define and communicate global priorities across diseases	1	
2	Prioritization Forum Up to US\$ 5 m	Review funding directions with donors and evaluate if funding is aligned with global priorities	3	
3	~US\$ 15 m (small) 	Fund 3-4 projects (no innovation- focused projects)	3 	3 repurposed drugs - simple
4	~US\$ 50 m (PDP size) 	Fund 15-20 projects (few innovation-focused projects)	9 	1 new chemical entity (NCE) - simple
5	~US\$ 100 m (medium) 	Fund 25-40 projects (including ~5 innovation- focused projects)	14 	1 repurposed drug - complex
6	~US\$ 300 m (large) 	Fund 80-100 projects (a novel intervention to approval)	26 	1 simple biologic
7	>US\$ 500 m (global) 	Fund 140-160 projects (can fund many projects in priority areas)	40 	1 NCE - complex

Figure 1: The TDR report explores options for pooled funds of varying sizes and models their output. The underlying assumptions are based on a mixed innovation model, which reaps low-hanging fruits (repurposed drugs) but also invests in more basic research to understand disease principles and tailor interventions (e.g. complex NCEs). Furthermore, the annual fund sum is slowly increased and would reach the size given in the table only in 2027. The development pipeline fills up slowly, and considerably more products would be registered in the 10 years after 2030 than in the initial phase up to that point. The underlying development costs are explained in Table 1 and Box 3. Source: "Health Product Research & Development Fund: A Proposal for Financing and Operation" UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (Geneva, 2016).

d) Supranational R&D organization

Another option for joint funding would be to establish a supranationally governed organization that carries out research. One example of this type of organization is the European Organization for Nuclear Research (CERN; Annex 1, Box 12). CERN is set up by an international convention through the United Nations Educational, Scientific and Cultural Organization (UNESCO) that requires ratification, and which gives CERN the status of an international organization similar to WHO.

One major reason for the international collaboration to create CERN was the necessity of huge investment into a central infrastructure that no country could have reasonably financed alone. This is not required in pharmaceutical R&D: while biosafety level 4 laboratories are expensive to construct and maintain, the required capacity can be decentralized throughout different countries. Without owning any laboratories, product development partnerships such as DNDi

have successfully developed drugs including new formulations and combination therapies for malaria, Chagas disease and visceral leishmaniasis³⁰.

There is already one example of a supranational organization in biomedical research: the European Molecular Biology Laboratory (EMBL; see Annex 1, Box 14) was established by an international treaty. There might be a case for such a facility in immunization R&D, allowing the use of different platform technologies to develop vaccine candidates for a variety of pathogens. Similarly to the EMBL, this could consist of a network of decentralized R&D entities.

Summary of R&D preparedness financing

There are a number of possibilities that could improve the efficiency of current and future spending on research. Which model is most appropriate will also depend on the priorities identified by workstream 2. Improved coordination through options (a) or (b) above could be implemented relatively soon and easily without any formal international agreement.

One possible option could be to convince countries to make commitments for preparedness for one or more specific pathogens, with WHO monitoring progress. WHO's Global Observatory on Health Research and Development already provides a useful platform through which to monitor increases in funding of these decentralized mechanisms. This could be done in collaboration with the G-Finder survey, which has been tracking global financial flows into R&D on neglected diseases for several years and which included Ebola for the first time in 2014. The option of establishing a pooled funding mechanism coupled with a sustainable innovative financing model and a wide scope could be pursued in parallel, and is explored in detail in the recent TDR report¹⁵.

The Oslo Consultation focused on the need for increased investment in R&D; it discussed more broadly the option of leveraging new and existing financing and structures for R&D preparedness and response through a new global mechanism. Such a mechanism could finance and coordinate R&D for both preparedness and emergencies. At the consultation it was discussed that a host entity for such a new mechanism should meet a number of specific criteria³¹.

The WHO Global Observatory on Health Research and Development (R&D) should facilitate information sharing with a view to helping identify gaps and opportunities for health R&D and providing the information necessary to define priorities and potential target product profiles (TPPs) for R&D investments based on public health needs.

3.2 Funding of emergency response R&D

Funding of R&D as part of an emergency response is different from funding R&D for preparedness, in that the necessary resources must be rapidly available when an emergency hits. In the case of an outbreak, substantial funds usually become available only after a while;

³⁰ <http://www.dndi.org/about-dndi/key-accomplishments/>

³¹ Outcome document: *Financing of R&D preparedness and response to epidemic emergencies*, page 4. Oslo, October 29-30, 2015. <http://www.who.int/medicines/ebola-treatment/Outcome.pdf>

thus the key parameter for emergency funding is not size, but reactivity. This enables starting clinical trials where candidate products are available; immediate assessment of whether existing products can be repurposed; and the commencement of necessary operational research to understand the disease better. A key aspect in this context is the need for rapid coordination, and clarity as to who makes decisions on clinical trial protocols, promising candidates for repurposing, and/or data collection protocols. These questions will be dealt with in workstream 3, but are closely linked to the financing of this kind of research. As for preparedness funding, there are various options, ranging from increased coordination to pooled emergency funds.

a) Better coordination through joint programming

In response to an outbreak, different actors usually launch separate research responses. This leads to duplication and does not make efficient use of existing R&D money. One possible solution to this problem is for research funders to issue joint calls on agreed R&D priorities, with each funder retaining control over its individual budget. Although this could lead to more efficient use of funds, a higher level of coordination is likely to lead to further delays in the research response, as the total time needed for this process will be that of the slowest member of the funder group.

b) Anticipated joint research calls

One possible means of overcoming longer lead times due to increased coordination efforts is anticipated joint research calls. For these, separate proposals for emergency research for different diseases are developed in advance of an outbreak. These ready-made plans are then kept on hold, and can be implemented quickly in case of an emergency. Decisions on how to use funds remain with individual institutions. The pre-planned proposals allow for a rapid response—but it remains to be assessed how well such proposals can be adapted to actual outbreaks in advance, and how much immediate change to them would be necessary in an emergency.

c) Contingency reserves – pooled funds for emergencies

As for R&D preparedness, a pooled fund could be an effective mechanism to increase research coordination. Such a fund would rely on only a single decision-making authority, allowing for rapid response, which is crucial during an outbreak. The report of the Commission on a Global Health Risk Framework for the Future³² states that “it makes sense to have contingency financing arrangements in place to ensure a rapid and effective response”. Financing of such a contingency fund could be done through the voluntary or mandatory contributions of its members.

One example of such a mechanism is the WHO Contingency Fund (Annex 1, Box 11); however, the WHO Secretariat’s proposal upon which the World Health Assembly based its decision to establish the Contingency Fund explicitly states that it is not intended to fund substantive

³² *The neglected dimension of global security*. Report of the Commission on a Global Health Risk Framework for the Future, January 2016. <http://nam.edu/wp-content/uploads/2016/01/Neglected-Dimension-of-Global-Security.pdf>

research and development. The argument was that R&D requires greater financial investment than contemplated in this context, as well as active and long-term partnership. The fund's financial means are limited (US\$100m) and the inclusion of R&D could lead to competition with other emergency response measures, especially since the fund is not limited to disease outbreaks but also covers other emergencies with health consequences, such as conflicts or natural disasters. The most important limitations with regard to financing R&D activities are, however, the duration and scope of the fund, which is meant to cover measures only for up to three months after the declaration of an international emergency, and is limited to WHO response and cannot therefore be used to fund entities outside WHO.

Option (d) describes a special form of contingency fund. An insurance-based model such as the World Bank Pandemic Emergency Facility (option (e)) could also be used to fill such a fund.

d) Draw down emergency accounts

One option by which to finance an immediate R&D response would be a dedicated fund to which donors commit to release certain financial resources in an outbreak situation. This approach has the advantage that the resources remain with the respective funder and are only disbursed in the event of an emergency. All legal arrangements have to be made upfront to allow for immediate use of the resources, including clear identification of who has the power to authorize the use of the funds. The WHO contingency fund allows this kind of contribution.

e) World Bank Pandemic Emergency Facility (PEF)

Most discussions on pooled funding mechanisms aim to assemble financial contributions from different sources. The planned World Bank PEF, while having the character of a centralized funding mechanism that can pool financial resources, is linked to a complimentary financing mechanism that consists of an insurance-based bond model (Annex 1, Box 13). Countries can buy insurance that bears the cost of interventions to respond to an outbreak. Payment of premiums finances a bond that is readily available for disbursement of money in the event of an outbreak that fulfils certain defined criteria (a “trigger event”). Unlike WHO's Contingency Fund, the PEF is limited to disease outbreaks and can disburse to different entities including but not limited to WHO.

Summary of funding of an R&D response in an emergency situation

Financing an R&D response in an emergency requires immediately available funds. Fund availability could in principle be assured by a mechanism for pooled funding, as with preparedness, but such a mechanism would need to be agile enough to disburse funds immediately, without lengthy procedures. The WHO Contingency Fund does not seem to be an adequate instrument as its scope is too limited. The PEF, in comparison, could advantageously include R&D response measures, as this would at least partly cover the gap for those outbreaks that trigger the insurance solution. Any pooled funding or joint programming mechanism could also cover R&D response if it foresees a specific mechanism that allows very rapid disbursement of funds for specific R&D (e.g. vaccine trials or R&D into the causal relationships or ways of transmission).

Better coordination among R&D stakeholders, in particular during an emergency, could be achieved through identification of a mechanism to facilitate real-time sharing of information

about which R&D activities are ongoing, planned and/or funded. The GloPID-R network might provide a platform for such coordination among funders of R&D. One of the aims of GloPID-R, which promises to react within 48 hours of a significant outbreak³³, is to bridge the gap between long-term financing from conventional research calls and quick financial support for urgent research needs.

Part 4: Options to leverage industry contribution through market shaping

International public health emergencies are uncertain and unpredictable in nature and can happen in many different contexts and countries. Preparing for them is a collective challenge. If countries wish to be better prepared—and there certainly is an investment case for this (see 2.2)—they will not be able to achieve this on their own. An internationally coordinated intervention is required to share risks, rewards and resources, as with health insurance schemes to achieve universal health coverage (UHC). Such an initiative would ideally bring together funding from public, private and philanthropic sources, as separate sectors cannot deal with R&D preparedness alone.

As outbreaks due to highly infective emerging pathogens only happen sporadically, the traditional market-based model does not provide sufficient incentive for pharmaceutical companies to invest in countering these pathogens. Innovative measures to harness the private sector are already starting to be implemented in different areas, and are discussed in the following paragraphs on market shaping. There may also be a window for contributions from the private sector, as outbreaks often have negative effects on economies, including large companies (see Box 5).

4.1 Market shaping

Organizations such as UNITAID and Gavi have created sustainable markets that trigger investment into product development (market shaping). A purchase commitment to procure a certain number of dosages of a vaccine or medicine against a specific pathogen or set of pathogens could create sufficient incentive for the private sector to develop and produce such a vaccine. Such a commitment would either require a mechanism that could centrally procure such products, or would rely on pooling the demand of individual buyers in order to create a sufficiently large incentive. This instrument has been tested with respect to vaccines and medicines—for example for paediatric HIV drugs.

For the sporadically occurring diseases discussed in this document, purchase commitments can also be made by stockpiling vaccines or medicines either physically or in a virtual manner. In the latter case the investor commits money to be used for R&D that is then offset against any product purchases in case of an outbreak. Such a deal was agreed upon recently by Gavi and Merck Sharp & Dohme (MSD): Gavi committed US\$5m to the development of MSD's VSV-EBOV

³³ <http://www.glopid-r.org>

Ebola vaccine³⁴; in return, MSD has to make 300,000 doses of the vaccine available for use in emergencies and further clinical trials, and submit a licensing application until the end of 2017. The US\$5m will be offset against any purchases Gavi will effect once the vaccine is licensed.

A barrier to the use of such instruments is the fact that it is only possible to push vaccine or treatment candidates to Phase I safety trials, unless there are major outbreaks that allow for Phase II and III clinical trials to test efficacy. However, the testing and registration process is significantly less demanding for diagnostics in terms of costs, the number of patients needed, and time. Thus, purchase commitments might be especially effective for diagnostic candidates. One requirement for a purchase commitment would be that the company is able to demonstrate that they have the manufacturing capacity to meet demand in an outbreak.

Milestone prizes could be tested as another possible incentive for R&D on emerging pathogens. Such prizes could be defined for specific candidates that pass Phase I clinical trials, and which fulfil individual product target profiles as defined by workstream 2.

Purchase commitments and milestone prizes also have the advantage that they can help to delink the price of the final product from R&D costs, a step that has been identified as a crucial prerequisite when developing products for diseases that primarily affect the poor³⁵.

Box 5: Potential sources of finance for R&D identified by the Commission on a Global Health Risk Framework for the Future³⁶

1. **New direct contributions:** governments, foundations and the private sector could directly fund a dedicated R&D organization such as DNDi or the Medicines for Malaria Venture, which could then carry out the necessary R&D.
2. **National security R&D budgets:** pandemics are a major security threat. The US alone spends US\$ 70bn annually on R&D for security, mostly in military research.
3. **Existing public, philanthropic, and university R&D budgets:** prioritisation in the health arena could lead to increased allocation of funds to R&D on pandemic threats
4. **Pharmaceutical industry:** increased private R&D through market shaping
5. **New sources of private finance from outside the health care sector:** in the case of an outbreak economies often suffer, with negative effects on large companies. Some sectors are particularly affected, including insurance, travel, tourism and the meat and poultry industry. All these businesses have an economic interest in preventing pandemics. It is unclear, however, which mechanism could best ensure their contribution.

³⁴ <http://www.gavi.org/Library/News/Press-releases/2016/Ebola-vaccine-purchasing-commitment-from-Gavi-to-prepare-for-future-outbreaks/>

³⁵ *Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination*, 2012. http://www.who.int/phi/cewg_report/en/

³⁶ *The Neglected Dimension of Global Security*. Report of the Commission on a Global Health Risk Framework for the Future, January 2016. <http://nam.edu/wp-content/uploads/2016/01/Neglected-Dimension-of-Global-Security.pdf>

Part 5: Discussion and conclusion

The need for increased funding for R&D has been echoed by many expert groups, including the High-level Panel on the Global Response to Health Crises, the Commission on a Global Health Risk Framework, and the Independent Panel on the Global Response to Ebola. This need is further stressed by other authors^{37,38}. The Oslo consultation concluded that adequate and sustainable investment and new incentives are urgently needed to ensure appropriate funding for R&D preparedness and response. It also strongly encouraged participation of low- and middle-income countries in all actions designed to ensure better preparedness, and invited them to contribute, including through funds. The risk of future epidemics is shared among all countries.

R&D preparedness

Ideally, a new global mechanism should be devised to leverage more funding and improve coordination of existing financing for R&D preparedness and response, in order to ensure appropriate investment into R&D on the Blueprint pathogens. This mechanism should provide incentives for existing funders to coordinate their efforts, and ideally would include a financing facility offering the possibility of pooling funds. Table 2 summarizes the different models presented in this paper.

R&D response

Financing R&D during an emergency response requires a slightly different funding mechanism, one that ensures simple and quick availability of funds, unencumbered by bureaucracy. Such funding for emergency R&D could be ensured through any mechanism set up to finance and manage the general emergency response, or through an additional mechanism.

Similar to R&D preparedness, and independent from the question of financing, there is a need for better coordination of R&D during emergencies. This could be achieved through a mechanism that allows real-time sharing of information on which R&D activities are ongoing, planned, and/or funded. Table 2 summarizes different options discussed in this paper.

³⁷ Balasegaram, Manica, et al. *A global biomedical R&D fund and mechanism for innovations of public health importance. PLoS Med* 12(5) (2015): e1001831.

³⁸ Plotkin, Stanley A., Adel AF Mahmoud, and Jeremy Farrar. "Establishing a Global Vaccine-Development Fund." *New England Journal of Medicine* 373.4 (2015): 297-300.

Table 2: Summary of options for funding and increased coordination of preparedness and emergency R&D

Preparedness	Summary
Coordination on product/pathogen level	<ul style="list-style-type: none"> • Research is coordinated by a dedicated entity for each pathogen/product using tools such as technology roadmaps • No pooling of funds
Open coordination/joint programming	<ul style="list-style-type: none"> • Priority setting across different diseases • Projects are aligned according to a research strategy • Control of individual research projects remains with funder • No pooling of funds
Pooled financing global level	<ul style="list-style-type: none"> • Single mechanism that pools funds to share risks and cost of funding R&D • Can be used for emergency R&D as well, but requires a specific disbursement mechanism • Financing mechanism needed
Supranational R&D organization	<ul style="list-style-type: none"> • International organization based on international treaty • Financing mechanism needed
Rapid response	
Joint programming	<ul style="list-style-type: none"> • Projects are aligned according to a research strategy • Control of individual research projects remains with funder • No pooling of funds
Anticipated joint research calls	<ul style="list-style-type: none"> • Ready-made research plans for different diseases are developed in advance of an outbreak
Contingency reserve	<ul style="list-style-type: none"> • Pooled fund for emergencies, rapidly deployable upon trigger event
Draw down emergency accounts	<ul style="list-style-type: none"> • Funders commit to pay to a contingency reserve, but resources remain with them until needed
World Bank Global Pandemic Emergency Facility	<ul style="list-style-type: none"> • R&D should be included • Linked to an insurance-based bond model • Creates discipline via linkage to country level emergency preparedness plans

To agree and set up an international mechanism that brings increased R&D funding and coordination will require some time and largely depends on the political commitment of WHO Member States.

In the meantime, however, and as the current Zika outbreak shows, there is a clear need for decisive short-term action. As part of the Blueprint, WHO is committed to bridging this time gap in the most effective manner possible, working closely with existing mechanisms such as GloPID-R. In the further implementation of the Blueprint, the pilot project on research coordination on a pathogen level for MERS-CoV and the experience gained with R&D coordination on the development of malaria vaccines (see Annex 1, Box 8) will serve as role models. This model—relying on the outputs of the other workstreams of the Blueprint—includes the following two main elements.

1. Convening regular meetings of key funders and researchers to increase funding and coordination

For MERS-CoV, an R&D consultation was convened by WHO in December 2015. The key stakeholder group comprises BARDA, the US National Institute of Allergy and Infectious Diseases (NIAID), the International Vaccine Institute (IVI), the Wellcome Trust, the European Commission Directorate-General on Research & Innovation, the GloPID-R network of funders coordinated via the European Commission, and the Bill and Melinda Gates Foundation. This group drafted an R&D roadmap³⁹ that identifies gaps and capacity needs, and articulates goals ranging from basic research to capacity building for production. The draft roadmap points out urgent areas in basic research that need more attention, including different aspects of camel vaccination (camels are a major reservoir for the virus), immune correlates of protection, pathogen diversity, and outbreak modelling. A better understanding of the disease will enable more informed development of technologies, and could lead to the identification of possible innovative interventions such as a vaccine for camels, which is one of the priorities in the MERS-CoV roadmap.

The document sets further specific timeline goals for entry into clinical trials, and calls for early development of capacity for clinical trials, laboratory testing, and manufacturing. The document emphasises enabling technologies, tools and processes that cut across specific products, including improved animal models, the standardization of laboratory procedures and reagents, and target product profiles for diagnostics, vaccines and treatments. The roadmap is the key guiding document for monitoring MERS-CoV R&D.

Progress will be assessed and the roadmap adapted accordingly through annual physical meetings of the key stakeholders, supplemented by quarterly teleconferences.

³⁹ Draft: *A Roadmap for Research and Product Development against Middle East Respiratory Syndrome-Coronavirus (MERS-CoV)*. <http://www.who.int/csr/research-and-development/rd-mers-roadmap.pdf?ua=1>

2. Facilitating communication and exchange of information and samples and the identification of research gaps, as well as unsuccessful approaches, through a central knowledge hub, the WHO Global Observatory on Health Research and Development

Such a central knowledge hub could include⁴⁰:

- (i) A registry of all field R&D projects, comprising project summaries and timelines; contact details; funding details; and categorizations of how the projects fit into the R&D chain
- (ii) A registry of failed research projects, to avoid duplication of errors
- (iii) A list of R&D needs, to help funders prioritize their research
- (iv) A database of active compounds and specimens, to allow easy sharing of same. Ideally compounds and specimens would also be physically available, in a model similar to that of the Malaria Box provided by the Medicines for Malaria Venture.

This hub will contribute to the identification of gaps and opportunities for health R&D, and provide necessary information when defining priorities and potential target product profiles for new R&D investments based on public health needs.

⁴⁰ Based on: Årdal C, Røttingen J-A. *An open source business model for malaria*. PLoS ONE 10 (2) (2015): e0117150.

Annex 1

Box 6: EU Joint Programming Initiative on Antimicrobial Resistance

The European Union Joint Programming Initiative on Antimicrobial Resistance (AMR) has been set up to pool national research efforts to spend public R&D resources more efficiently. Joint Programming is used in different areas to overcome the fragmentation of national research programmes, in particular for challenges that are global in nature. The development of new preventive and therapeutic approaches is only one of many areas that form part of the Initiative. Research priorities are set out in the strategic research agenda, which is implemented through launching joint calls for proposals to facilitate cross-border research projects⁴¹.

Box 7: GloPID-R - Global Research Collaboration for Infectious Disease Preparedness⁴²

GloPID-R is a network of 23 funding organizations investing in research related to new or re-emerging infectious diseases. The goal of GloPID-R is to facilitate an effective research response within 48 hours of a significant outbreak of a new or re-emerging infectious disease with pandemic potential. GloPID-R works to build the research capacity and capabilities necessary to conduct the required scientific research in the event of an outbreak. It is not itself a funding organization, but it aims to make the work of its members more effective through collaboration and by jointly addressing the barriers to emergency research.

GloPID-R aims to:

- Address scientific, logistical, legal, regulatory, ethical and financial challenges to the rapid mounting of such a response
- Establish a strategic agenda to address the above-mentioned challenges and identify gaps; this should lead to the building of sound research capacity to ensure a rapid international research response in the event of an outbreak
- Facilitate the exchange of information between funders
- Connect existing and future research networks in this area.

GloPID-R is chaired by the European Commission together with Brazil, Canada, France, South Africa, and South Korea.

Box 8: The Malaria Vaccine Funders Group

The Malaria Vaccine Funders Group consists of technical focal points within the Wellcome Trust, National Institutes of Health, Bill and Melinda Gates Foundation, United States Agency for International Development, European Commission, European and Developing Countries Clinical Trials Partnership, and European Vaccine Initiative. It is facilitated by the World Health

⁴¹ <http://www.jpamr.eu>

⁴² <http://www.glopid-r.org/>

Organization. It was established in order to exchange information and opinions between internationally active funding bodies for malaria vaccine development, with the hope that progress could be accelerated. The group's work aims to facilitate the coordination of vaccine research activities by defining and making use of synergies between ongoing and planned programmes/activities, structuring and prioritizing vaccine research efforts. Through this the group aims to reduce unnecessary overlaps and identify research needs where support can be assembled in a complementary manner. The group's activities are guided by the Malaria Vaccine Technology Roadmap, which enables a joint planning framework for R&D within which agencies individually implement funds according to their own scope. The funders group meets face to face at least once a year, or more often when needed. This process has been running for over 10 years, and has proven to be sustainable and desirable for all agencies involved, particularly as it enables an ongoing global gap analysis.⁴³

Box 9: Recent proposals to set up pooled funding mechanisms

Proposal for a Global Biomedical R&D Fund

A group of authors recently suggested the creation of a global R&D fund and mechanisms that promote coordination, collaboration, and utilization of new and innovative incentives for R&D on antimicrobial resistance, emerging infectious diseases, and neglected diseases. To be functional the Fund would require a global umbrella framework for financing and coordinating R&D to address global needs and gaps based on defined target product profiles. The Fund would combine traditional mechanisms of funding (e.g. grants) and less traditional incentives (e.g. prizes) and ensure equitable access to any new products. The authors call for a specific R&D financing mechanism linked closely to an entity with the ability to monitor research flows and outputs. The mechanism would essentially be publicly financed by governments.⁴⁴

The Global Vaccine Development Fund

The Global Vaccine Development Fund, as proposed by a group of authors, is a \$2bn global fund to prevent infectious diseases that are not attractive to major manufacturers because anticipated revenues of commercial vaccine development would be too small. The fund would be supported by governments (50 per cent) and foundations and pharmaceutical companies (50 per cent). It would cover the phases between vaccine discovery and late-stage development, and, in the end, help make vaccines available for emergency use. As for the organization, a small structure is proposed to manage fundraising, fund distribution and the decision-making process.⁴⁵

⁴³ http://www.who.int/immunization/topics/malaria/vaccine_roadmap/en/
http://www.who.int/immunization/topics/malaria/malaria_vaccine_funders_group/en/

⁴⁴ Balasegaram, Manica, et al. *A global biomedical R&D fund and mechanism for innovations of public health importance*. *PLoS Med* 12(5) (2015): e1001831.

⁴⁵ Plotkin, Stanley A., Adel AF Mahmoud, and Jeremy Farrar. Establishing a global vaccine-development fund. *New England Journal of Medicine* 373.4 (2015): 297-300.

Box 10: WHO Pooled Fund for Type II and III diseases and the specific research needs for developing countries in relation to type I diseases

The CEWG report highlighted the continuing failure of existing market and public mechanisms to support research and develop technologies to combat diseases that predominantly affect developing countries. Its recommendations included a call to improve the identification of health priorities, coordinate global efforts around these priorities, and establish new, innovative and sustainable sources of funding to support R&D for product development in these areas. Subsequently the World Health Assembly decided to create the Global Health R&D Observatory in order to monitor and map global health R&D. A coordinating group will use analysis from the Observatory to identify priority health issues. The WHO Voluntary R&D Fund, if finally set up, will finance R&D in those priority areas. TDR was selected as the most suitable existing body to manage the process of selecting, funding and monitoring progress in the R&D projects supported by the Fund. Following a request from the World Health Assembly, TDR has recently published its report exploring options for a financial mechanism for health product R&D under the governance of WHO.⁴⁶

Box 11: WHO Contingency Fund

In May 2015 the World Health Assembly decided to create a replenishable contingency fund for rapid scale-up of WHO's initial response to outbreaks and other emergencies with health consequences. The target capitalization is US\$100m, fully funded by voluntary contributions. The Fund will not only bridge financing for WHO response measures for outbreaks of infectious diseases, but also for other emergencies such as earthquakes or floods.

Box 12: CERN

CERN, established in 1954, was created by a convention through UNESCO with the purpose of strengthening European research competencies. CERN has an annual operating budget of more than US\$1bn, which is provided by the 21 ratifying countries based on each country's GNP. The split therefore varies from year to year, but the principle remains the same in that countries with larger economies contribute correspondingly larger portions of the operational budget. This budget covers only operational costs such as running the laboratory and other facilities and the salaries of administrators, but not the salaries of the physicists analysing the data. Those salaries are paid by countries—i.e. Norway pays the Norwegian scientists' salaries. The operational budget also does not cover the building of major projects such as the Large Hadron Collider (LHC). This was paid for separately through country contributions, including significant

⁴⁶ "Health product research & development fund: a proposal for financing and operation"
UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
(Geneva, 2016). http://apps.who.int/iris/bitstream/10665/204522/1/9789241510295_eng.pdf?ua=1

contributions from Japan and USA, even though these were not ratifying countries. Non-ratifying countries have contributed generously to the building of the LHC because their scientists are also allowed to carry out experiments at CERN, and they also benefit from the increased level of knowledge that the organization produces. CERN has a policy of open access and open data.

Box 13: World Bank Pandemic Emergency Facility

The World Bank is currently working on a new instrument to finance efforts to contain dangerous epidemic outbreaks before they turn into pandemics by channelling funds to governments, multilateral agencies, nongovernmental organizations and others. This instrument is the so-called Pandemic Emergency Financing Facility (PEF). Financing from the PEF will be linked to strong country-level epidemic and pandemic emergency preparedness plans, thereby incentivizing recipient governments and the international community to introduce rigour and discipline into crisis preparedness. The PEF is currently expected to cover a variety of response activities, including rapid deployment of:

- A trained and ready health work force
- Medical equipment, pharmaceuticals and diagnostic supplies
- Logistics and food supplies
- Coordination and communication.

The PEF does not cover pandemic preparedness or reconstruction efforts. Whether the PEF would cover R&D as part of the emergency response is still under discussion.

Box 14: The European Molecular Biology Laboratory (EMBL)

The EMBL was established in 1974 by 10 European states as an instrument through which to cooperate in fundamental research, development of advanced instrumentation and advanced teaching in molecular biology, as well as other areas of related research. Its focus is on work not normally or easily carried out in national institutions, and one goal of its creation was to bundle research capacities in Europe in order to compete with US research entities. The Laboratory was founded as an intergovernmental institution based on an international agreement. By 2015, 21 countries are members of EMBL and have to contribute annually to EMBL's expenditure according to their net national income. In 2011, EMBL had a budget of €171 million, 55 per cent of which came from regular contributions of Member States. The rest was generated from additional gifts from member states, private organizations and individuals.